

inquiry into the archaic minutiae of history."

The most commonly accepted version of the signal¹⁻³ is that given by Dr F W H Turnbull (29 April, p 1147): "England expects that every man will do his duty." The version including the words "this day" (Mrs J Wilkinson, 13 May, p 1280) originates in a letter written by Lt Humphrey Senhouse (third lieutenant of the *Conqueror*) to his mother six days after the battle. Captain Blackwood (of the *Euryalus*), writing home the day after the battle, gave the signal as: "England expects every officer and man will do their utmost duty." Admiral Lord Collingwood (second-in-command of the fleet at Trafalgar) had a highly individual version engraved on a ring: "England expects everything: men, do your duty."³

The version I quoted (8 April, p 905), "England expects every man to do his duty," is given in the *Oxford English Dictionary* under "expects" and is taken from the biography of Lord Nelson by the Poet Laureate, Robert Southey,⁴ published in 1813. All these versions differ from the one on the south facade of the plinth of Nelson's column in Trafalgar Square: "England expects every man will do his duty."

Richard Asher's plea was not in vain—I did look up everything I quoted.

I am grateful to Mr Timothy Wilson of the National Maritime Museum, who, I hope, got as much pleasure out of this research as I did.

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¹ Bryant, Sir Arthur, *Nelson*. London, Collins, 1970.
² Carr, H G, *Flags of the World*, revised edn. London, Frederick Warne, 1961.

³ Mead, H P, *Trafalgar Signals*. London, Percival Marshall, 1936.

⁴ Southey, R, *The Life of Nelson*. London, Frederick Warne.

* **This correspondence is now closed.—Ed, *BMJ*.

Fluorouracil cardiotoxicity

SIR,—We should like to agree with the view expressed by Dr A Pottage and others (4 March, p 547) that chest pain subsequent to the administration of 5-fluorouracil is a rare but genuine complication. In the treatment of a comparable number of cases to that described by Dr Pottage and his colleagues we have seen two such complications attributable to 5-fluorouracil. Both patients were on single-agent therapy for adenocarcinoma of the colon, and in both cases pretreatment electrocardiogram and serum enzyme activities—enzyme aspartate transaminase, adenine transaminase, and lactate dehydrogenase—were normal. Neither patient had a past history of angina or of hypertension.

A 65-year-old woman developed severe central chest pain several hours after the sixth intravenous bolus of 5-fluorouracil 20 mg/kg. She had concomitant features of sweating, nausea, vomiting, and dyspnoea. Despite therapy she rapidly developed cardiogenic shock and died. The ECG showed evidence of an acute transmural anterolateral myocardial infarction. Necropsy was refused.

A 43-year-old man developed severe central chest pain radiating into the left arm seven hours after his second bolus of a five-day course of intravenous 5-fluorouracil 15 mg/kg. The pain was unrelieved by glyceryl trinitrate but responded to diamorphine. The ECG showed some ST depression, the cardiac enzyme activities remaining within

normal limits. Four days later a further intravenous bolus of 5-fluorouracil was given at a dosage of 10 mg/kg. Once again central chest pain occurred, but on this occasion was much less severe.

It is of interest that neither of these patients had received myocardial irradiation, in contrast to the patients reported by Dr Pottage and his colleagues. As 5-fluorouracil is known to be a radiosensitiser this may have been of importance in the Edinburgh patients. A complication with this severity of symptoms and possible fatal results requires to be widely recognised. Further investigation of the underlying mechanism is required.

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Tryptophan dosage critical for its antidepressant effect

SIR,—A recent leading article (29 October 1977, p 1105) focused on the dose used as one critical determinant of the therapeutic effect of tryptophan in depression.² We have just completed a double-blind controlled study comparing the antidepressant effect of tryptophan-nicotinamide with that of imipramine, the results of which could help to elucidate the dose-effect relationship of tryptophan. In a pilot study we found tryptophan-nicotinamide to have an antidepressant effect in seven of 11 newly admitted depressed patients.¹ Nicotinamide was given to reduce the breakdown of tryptophan by the tryptophan pyrrolase in the liver.²

The study population consisted of 25 newly admitted severely depressed patients with a diagnosis of primary affective disorder according to Feighner's criteria.³ Medications were administered under double-blind conditions for a period of four weeks. The tryptophan-nicotinamide dose schedule consisted of 2 g/day L-tryptophan and 0.5 g/day nicotinamide for the first week, 4 g/day L-tryptophan and 1.0 g/day nicotinamide for the second week, and 6 g/day L-tryptophan and 1.5 g/day nicotinamide thereafter and was given in equal doses at 8 am and 8 pm. Imipramine was given in a single dose at bedtime of 75 mg/day for the first week, 150 mg/day for the second week, and 225 mg/day thereafter. A third group received all three drugs to determine whether tryptophan-nicotinamide could potentiate the action of imipramine.

Although the therapeutic effect of tryptophan-nicotinamide did not differ significantly from that of imipramine, the mean scores on the Hamilton and Beck rating scales showed that its efficacy tended to diminish after two weeks when the dose of tryptophan was increased from 4 to 6 g/day and that of nicotinamide from 1 to 1.5 g/day. This is consistent with the results of two studies by Herrington *et al*^{4,5} in which an increase in the tryptophan dose from 6 to 8 g per day (without nicotinamide) at the end of the second week was associated with a decline in the therapeutic effect. The higher doses may have led to levels of brain tryptophan that were too high.

Clinical improvement and increase in plasma tryptophan levels were significantly and positively correlated for patients treated with tryptophan-nicotinamide ($r_6 = 0.72$, $P < 0.05$ for decrease in Beck total score and increase in free plasma tryptophan). However, they were negatively correlated for patients treated with the tryptophan-nicotinamide-imipramine combination ($r_7 = -0.85$, $P < 0.01$), suggesting that tryptophan levels were too high in some of these patients. The study included patients with both unipolar and bipolar types of depressive illness and tryptophan-nicotinamide-imipramine was the only treatment efficacious for bipolar patients. Thus it seems that

high dosages of tryptophan are therapeutic in bipolar depressive illness.

The data suggest that there is an optimum range ("therapeutic window") for plasma tryptophan concentration and that the therapeutic response will decline above or below this range. The optimum range probably occurs at a lower plasma tryptophan level when tricyclic antidepressants are also given. Finally, we should like to make some tentative suggestions: (1) The therapeutic daily dose of L-tryptophan when given alone should be 6 g or below for patients with unipolar depression; for bipolar depressed patients it should probably be above 6 g. (2) If the tryptophan is given with nicotinamide the maximum daily dose should be no more than 4 g for unipolar patients and above 4 g for bipolar depressed patients. (3) If tryptophan is given with tricyclic antidepressants the dose of tryptophan should be halved for unipolar patients. (4) To minimise fluctuations of plasma tryptophan throughout the day and keep it within the therapeutic range the tryptophan should be given in divided doses; a twice-daily regimen appears adequate when tryptophan is given with nicotinamide. We think that under these conditions tryptophan will be as effective as tricyclic antidepressants when given alone and potentiate their action when given in combination. A full report of our study is in preparation.

This work was supported by the Medical Research Council of Canada, MA 5727.

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¹ Chouinard, G, *et al*, *Lancet*, 1977, 1, 249.

² Young, S N, and Sourkes, T L, *Lancet*, 1974, 2, 897.

³ Feighner, J P, *et al*, *Archives of General Psychiatry*, 1972, 26, 57.

⁴ Herrington, R N, *et al*, *Lancet*, 1974, 2, 731.

⁵ Herrington, R N, *et al*, *Psychological Medicine*, 1976, 6, 673.

Discord at Dulwich

SIR,—How wet can you get? Your leading article "Discord at Dulwich," (29 April, p 1094) ends with the advice that "the unhappy events in Dulwich... are a warning to all NHS staff. They should heed it:... doctors and nurses when tempted to deliver authoritarian commands to staff."

Discipline is necessary in all walks of life and it is never more necessary than in situations such as operating theatres where it is often necessary to give a command or an order requiring instant and unquestioned action. The surgeon gives an authoritarian command when he requires an instrument or a swab or requires a surgical assistant to hold a retractor a certain way or clip off a bleeding vessel. Unless such actions are done without question tragedy could result. This discipline applies all the way down the line and it is just as important for the porter to obey commands as any other member of staff.

So please show backbone and stand up for the doctors and nurses who are leaders of the hospital staffs, whether it be in the theatre, the ward, or the casualty department. There is nothing weak in accepting and acting on a command; the weak ones are those who